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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/905,056
Filing Date: July 12, 2001
Appellant(s): ASHKENAZI ET AL.

Leslie Mooi
For Appellants

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06 January 2006 appealing from the Office action mailed 23 December 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. Two applications related to the instant application were allowed. U.S. Serial No. 09/902,736 (claiming antibodies that bind PRO331) and U.S. Serial No. 09/909,064 (claiming nucleic acids that encode PRO 331) were allowed based upon an asserted utility that is different from the one relevant to the activity limitation recited in the instant claims.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct. Of course, the examiner disagrees with the conclusion that the claimed invention is enabled for reasons that will be explained herein.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellants' statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct. It is noted that only claims 39-43 are on appeal. Claims 44-47 and 49-51 appear in the appendix, but are not on appeal as they have been indicated as being allowable.

(8) Evidence Relied Upon

The following ground(s) of rejection are applicable to the appealed claims:

Rampart et al., 1989, Am. J. Pathol. 135:21-25.

Hirahara et al., 1993, Thrombosis Res. 71:139-148.

Senger et al., 1983, Science 219:983-985.

Yeo et al., 1992, Clin. Chem. 38 :71-75.

Barsoun et al., 1997, J. Antimicrob. Chemother. 40 :721-724.

Szalai et al., 2000, J. Immunol. 164 :463-468.

(9) Grounds of Rejection

Claims 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to: (a) the amino acid sequence of SEQ ID NO: 292 (which is identical to the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209439), or (b) the amino acid sequence of SEQ ID NO: 292, lacking its associated signal peptide; which isolated polypeptide has the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells, does not reasonably provide enablement for other variants of SEQ ID NO: 292. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to isolated polypeptides having at least 80% amino acid sequence identity to: (a) the amino acid sequence of the polypeptide of SEQ ID NO: 292; (b) the amino acid sequence of the polypeptide of SEQ ID NO: 292, lacking its associated signal peptide; (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 292; or (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209439, wherein said polypeptide induces an inflammatory response. Hence, the claims are drawn to a genus of polypeptides having pro-inflammatory activity.

The specification does not teach the skilled artisan how to use such polypeptides. The specification discloses PRO331, the polypeptide of SEQ ID NO: 292. As an initial matter, it is noted that PRO331 tested positive in an assay measuring inhibition of VEGF stimulated endothelial cell proliferation and endothelial cell apoptosis. Since some polypeptides within the claimed genus also would reasonably be expected to have these activities (e.g., the preferred embodiment, the PRO331 polypeptide of SEQ ID NO: 292), the instant scope rejection properly indicates that those polypeptides are enabled, whereas other polypeptides within the genus that only have inflammatory response induction activity are not enabled for the following reasons.

The specification indicates that PRO331 tested positive in a skin vascular permeability assay at pp. 210-211. The specification asserts that molecules testing positive in this assay can be used in therapy where stimulation of an immune response is beneficial. In EXAMPLE 77, Skin Vascular Permeability Assay (Assay 64), a sample of purified polypeptide was injected intradermally into the backs of hairless guinea pigs. The resulting blemishes at the injection sites were measured, and the injection sites were subjected to histopathological analysis to detect infiltration of inflammatory cells. Injection sites with visible inflammatory cells (including neutrophilic, eosinophilic, monocytic or lymphocytic cells) were scored positive. The example does not disclose which inflammatory cells were observed for each PRO polypeptide testing positive in the assay. The skilled artisan would not conclude that a molecule testing positive in this assay was useful in any therapeutic method. The skilled artisan would conclude that a positive result in this assay indicates that the polypeptide is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic. See Barsoun et al. (1997, Journal of Antimicrobial Chemotherapy 40:721-724) who induce a hypersensitivity response in mice in a similar way to that done in instant Assay 64 (p. 722, "Delayed-type hypersensitivity assay"). In general, it is clear from the reference that such a response is not beneficial to the animal, as it indicates toxicity of the injected compound. Similarly, Szalai et al. (2000, Journal of Immunology 164:463-468).describe the Arthus reaction in guinea pigs using essentially the same assay as described in instant Assay 64 (p. 464, "Arthus reactions" and "Histology"). Again, the authors clearly indicate that a positive reaction in the assay

indicates that the injected substance is an irritant, or is toxic. Thus, a positive result in instant Assay 64 indicates that the polypeptide should not be administered therapeutically to a mammal, since it is toxic. Other toxins or irritants, such as lye or poison ivy extract, would also test positive in this assay. Lye and poison ivy extract are not considered to be therapeutically useful. Therefore, a positive result in the skin vascular permeability assay does not guide the skilled artisan as to how to use the claimed invention in its full scope.

Furthermore, isolated polypeptides at least 80% identical to the extracellular domain of PRO331 are not enabled by the specification. It is highly unlikely that the extracellular domain alone would test positive in any of the assays described, including the inhibition of VEGF stimulated endothelial cell proliferation and endothelial cell apoptosis assays, since an isolated extracellular domain is missing more than half of the full length or mature protein that was tested in any of the assays.

Due to the large quantity of experimentation necessary to determine how to use the claimed polypeptides other than as a polypeptide having the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells; the lack of direction/guidance presented in the specification regarding other uses, including uses related to vascular permeability activity or pro-inflammatory activity as discussed above; the absence of working examples directed to PRO331 polypeptides having specifically useful pro-inflammatory activities; the complex nature of the invention; the contradictory state of the prior art; the unpredictability of what activities any uncharacterized protein may have; and the breadth of the claims which fail to recite

useful functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(10) Response to Argument

Response to "Summary of the Arguments"

At pp. 4-6 of the Brief, Appellants submit a summary of their arguments. Specifically, Appellants argue that since the "how to use" prong of the enablement requirement under 35 U.S.C. § 112, first paragraph incorporates as a matter of law a requirement that the specification disclose a practical utility, the utility requirements under 35 U.S.C. § 101 are also addressed. Accordingly, a response to such remarks will be provided herein. However, it is important not to lose sight of the fact that the instant rejection is made under 35 U.S.C. § 112, first paragraph, regarding scope of enablement, and not under 35 U.S.C. § 101 for lack of utility.

From p. 4 to p. 5 of the Brief, Appellants argue that the data presented in Example 77, the Skin Vascular Permeability (SVP) assay (Assay 64, p. 210) of the specification and the cumulative evidence of record support a specific, substantial, and credible asserted utility for the claimed invention. Appellants argue that example 77 shows that PRO331 polypeptide tested positive in the SVP assay, allegedly demonstrating that PRO331 polypeptide induces inflammation in mammalian skin. Appellants urge that the SVP assay is well-recognized and widely accepted in the art. Appellants argue that the SVP assay was used to identify VEGF. Appellants submit that the claimed PRO331 polypeptides have utility as pro-inflammatory agents and therefore antibodies to such polypeptides are useful in the treatment of inflammatory

conditions. This has been fully considered but is not found to be persuasive. In the SVP assay, a polypeptide is injected under the skin of hairless guinea pigs. The resulting blemishes/blisters are measured and the injection sites are subjected to histopathological analysis to detect infiltration of various inflammatory cells, although the details of which cells were observed to infiltrate the blemish for each PRO polypeptide were not disclosed. A positive result in this assay would only indicate that the polypeptide is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a toxin or irritant. Barsoun et al. and Szalai et al. have been submitted as evidence in support of this characterization. Lye, poison ivy extract, or a splinter would produce positive results in this assay. Clearly, such substances are not considered of therapeutic value by the skilled artisan. Furthermore, it is noted that the specification only asserts that the polypeptides themselves are potentially of therapeutic use, not their antibodies. Finally, the specification has not established a causal relationship between PRO331 and any specific inflammatory response. For example, there is no evidence or assertion in the specification (or other evidence of record) that PRO331 mediates the inflammatory response to a specific event, such as viral infection. Therefore, the assertion that administration of an antibody to PRO331 could reduce inflammation is a flawed leap of logic.

In the second paragraph of p. 5 of the Brief, Appellants refer to the Rampart et al. publication as evidence that a similar assay was used to identify IL-8 as a mediator of acute phase inflammatory response to microbial stimulus and psoriasis. This has been fully considered but is not found to be persuasive. The Rampart et al. reference (Am. J.

Pathol. 135:21, 1989) discloses that IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin. The instant specification did not disclose which of four different type(s) of inflammatory cells were recruited by PRO331. Also, Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation. In this specific case, human PRO331 was found to be an irritant to guinea pigs. Such *might* indicate that PRO331 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO331, e.g. that the human PRO331 protein has an epitope that the guinea pigs were pre-sensitized to, or that PRO331 was an irritant to the guinea pigs (a result that is not surprising since it is a protein from a heterologous organism). In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO331. Accordingly, the only inflammation that could be treated using anti-PRO331 agents at the time the invention was made is that actually caused by PRO331, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting from excess PRO331 based upon

the results in the specification as originally filed). It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptides.

Appellants also refer to the declaration of Dr. Fong (submitted under 37 C.F.R. 1.132 on 30 September 2004). Appellants characterize the declaration as providing examples of important clinical applications for pro-inflammatory molecules in treating infections, and as establishing that inhibitors of pro-inflammatory molecules are useful to treat conditions where inflammation may lead to tissue destruction. This has been fully considered but is not found to be persuasive. The SVP assay, or Miles assay, discussed by Declarant, is useful as a preliminary screen for potential pro-inflammatory molecules. Basic irritants, such as poison ivy extract or spider venom, would test positive in this assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may be useful as a pro-inflammatory molecule. For example, MCP-1 and MCP-2 are not only positive in the Miles assay, they were also shown to have the specific activity of causing the extravasation of neutrophils. As Declarant points out, other CXC cytokines, while scoring positive in a Miles assay, have subsequently been shown to have specific activities of activating neutrophils or being chemotactic for T lymphocytes. Such information must be determined before one skilled in the art would know how to use PRO331; however, the specification does not disclose this information. The state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule is a pro-inflammatory molecule with specific activities, as opposed to a basic

irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound. For example, the Rampart reference (Am. J. Pathol. 135:21, 1989) used an assay similar to the one at issue, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation. Furthermore, Rampart et al. used FMLP as a reference chemoattractant and bradykinin as a reference neutrophil-independent mediator of increased microvascular permeability (p. 22, sixth paragraph of second column). No controls appeared to have been used in the SVP assay of the instant specificaiton.

At the paragraph bridging pp. 5-6 of the declaration, Appellants disagree with the examiner's position in previous Office Actions, stating that the appropriate evidentiary standard is a preponderance of the totality of the evidence. Appellants argue that the rejection must establish that it is more likely than not that one of ordinary skill in the art would doubt the statement of utility. This has been fully considered but is not found to be persuasive. The instant rejection is based upon consideration of the preponderance of the totality of the evidence, as will become apparent throughout this answer.

However, the issue is not whether or not the skilled artisan would be more likely or not to believe the asserted utility. The issue is whether or not undue experimentation would have been required of the skilled artisan to make and use the claimed invention. In the instant case, due to the large quantity of experimentation necessary to determine how to use the claimed polypeptides other than as a polypeptide having the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells; the lack of direction/guidance presented in the specification regarding other uses, including uses related to vascular permeability activity or pro-inflammatory activity as discussed herein; the absence of working examples directed to PRO331 polypeptides having specifically useful pro-inflammatory activities; the complex nature of the invention; the contradictory state of the prior art; the unpredictability of what activities any uncharacterized protein may have; and the breadth of the claims which fail to recite useful functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In the second paragraph of p. 6 of the Brief, Appellants point to the Fong declaration as establishing that a positive score in the SVP assay establishes utility for PRO331 polypeptides including treatment for inflammatory diseases such as autoimmune diseases, psoriasis, and others. Appellants urge that the specification, publications, and declaration would indicate to the skilled artisan that it is more likely than not that PRO331 polypeptides are useful to induce inflammation and PRO331 antibodies are useful to inhibit inflammation. Appellants refer to the utility guidelines as instructing the examiner that he/she must accept the opinion of a qualified expert based

on relevant facts whose accuracy is not being questioned, and that it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts. In the third paragraph of p. 6 of the Brief, Appellants conclude that the examiner has not made a prima facie case of lack of utility, and that the specification teaches the skilled artisan how to used the claimed invention. This has been fully considered but is not found to be persuasive. Since any irritant or toxin would test positive in the SVP assay, one skilled in the art would not be guided to use a substance testing positive in the assay to treat inflammatory disease. Also, just because a substance tests positive like an irritant or toxin in the assay does not mean that the substance plays a role in inflammatory disease. There is no evidence of record linking a change in amount or form of PRO331 with any specific inflammatory response in the body. Finally, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the fact sought to be established is whether or not a positive result in the SVP assay indicates a therapeutically important role for the tested substance. This is a fairly complex issue. Second, strong opposing evidence has been brought forth on the record that a positive result in the assay is a preliminary result,

since irritants and toxins also test positive in the assay and are not thought to be therapeutically useful as a result (Barsoun et al., Szalai et al., Rampart et al.). Dr. Fong is one of the inventors and has an interest in the outcome of the case, as opposed to a disinterested expert in the field. Finally, Dr. Fong bases his conclusions on facts. However, it is believed that the opposing evidence and scientific reasoning counterbalance the evidence contained in the declaration.

Response to "Response to Rejections"

A. The Legal Standard for Utility under 35 U.S.C. § 101

At pp. 7-10 of the Brief, Appellants discuss the legal standard for utility, with which the examiner takes no issue. Again, it is important not to lose sight of the fact that the instant rejection concerns scope of enablement under 35 U.S.C. § 112, first paragraph, and not lack of utility under 35 U.S.C. § 101.

B. Appellants argue that a *prima facie* Case of Lack of Utility Has Not Been Established

In the middle of p. 10 of the Brief, Appellants argue that the claimed PRO331 polypeptides induce an inflammatory response in the SVP assay, allegedly establishing a patentable utility for PRO331 polypeptides based on their ability to induce inflammation. Appellants characterize SVP as a dye-based pro-inflammatory cell infiltration assay in skin in which PRO331 induces mononuclear cell, eosinophil, and PMN infiltration into the site of injection. This has been fully considered but is not found to be persuasive. Example 77 (Assay 64), the SVP assay, appears at pp. 210-211 of the specification and reads as follows:

> This assay shows that certain polypeptides of the invention stimulate an immune response and induce inflammation by inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal. Compounds which stimulate an immune response are useful therapeutically where stimulation of an immune response is beneficial. This skin vascular permeability assay is conducted as follows. Hairless guinea pigs weighing 350 grams or more are anesthetised with ketamine (75-80 mg/Kg) and 5 mg/Kg xylazine intramuscularly (lM). A sample of purified polypeptide of the invention or a conditioned media test sample is injected intradermally onto the backs of the test animals with 100 µl per injection site. It is possible to have about 10-30, preferably about 16-24, injection sites per animal. One µl of Evans blue dye (1 % in physiologic buffered saline) is injected intracardially. Blemishes at the injection sites are then measured (mm diameter) at 1 hr and 6 hr post injection. Animals were sacrificed at 6 hrs after injection. Each skin injection site is biopsied and fixed in formalin. The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

Contrary to Appellants' statements, the specification does not show that PRO331 induces mononuclear cell, eosinophil, and PMN infiltration into the site of injection. Rather, since PRO331 tested positive in the assay, the specification indicates that PRO331 injection yielded "visible inflammatory cell infiltration into the skin" and "[a]t least a minimal perivascular infiltrate at the injection site." The inflammatory cells may be "neutrophilic, eosinophilic, monocytic or lymphocytic." There was no disclosure of *which* inflammatory cells were at the site, and how the PRO331 injection site compared to controls in terms of magnitude of immune response or types of immune cells recruited, or any other details. Again, injection of lye, poison ivy extract, bee venom, or even a splinter would have yielded a positive result in this assay as disclosed.

At p. 10 of the Brief, Appellants argue that the positive test results for PRO331 polypeptides in the SVP assay of Example 77 (Assay #64, pp. 210-211) are sufficient to establish patentability for the claimed polypeptides, in that the positive result indicates that the PRO331 polypeptides are effective to induce inflammation. Appellants summarize the SVP assay. This has been fully considered but is not found to be persuasive for the following reasons. As previously discussed, any irritant would yield a positive result in the SVP assay, and yet the skilled artisan clearly would not conclude that such irritants are useful pro-inflammatory molecules. Also, it is important to remember pp. 210-211 of the specification do not report the magnitude of the immune response for PRO331, what type(s) of immune cells were recruited by PRO331, or comparison to any controls. Also, only PRO331 of SEQ ID NO: 292 (the preferred embodiment), but no PRO331 variants as claimed, were tested. In the absence of such details, the skilled artisan would have to experiment unduly to determine how to use PRO331 polypeptides.

Beginning at the last paragraph of p. 10 of the Brief, Appellants provide five lines of argument to establish that a *prima facie* case of lack of utility has not been established. These will be addressed in turn to the extent that the arguments are relevant to the scope of enablement rejection under appeal.

1. Appellants allege that the art recognizes that the SVP assay is an in vitro *assay useful for identifying compounds with inflammatory activity* in vivo.

Appellants argue that the SVP assay has been widely accepted in the art. Appellants rely upon Rampart et al. as allegedly using a rabbit skin neutrophil accumulation assay

similar to the instant SVP assay to identify IL-8. Appellants state that, under pro-inflammatory conditions, several mechanisms act synergistically to mediate an increase in neutrophil accumulation, plasma extravasation, etc. Appellants argue that such events occur, for example, during the acute phase of an inflammatory response to a microbial stimulus or during pathologic conditions like graft rejection, edema, psoriasis, arthritis, tissue injury, etc. Appellants characterize Rampart et al. as suggesting the involvement of endogenous IL-8 in an acute phase inflammatory response of an animal to a microbial stimulus, and further disclosing suggestive data supporting its involvement in psoriasis (at p. 24, col. 1, last paragraph). Appellants reason that subsequent data affirmed the involvement in IL-8 in several inflammatory conditions and in immune response, e.g., rheumatoid arthritis, asthma, leprosy, inflammatory bowel disease, atherosclerosis, cystic fibrosis, and respiratory syndromes. This has been fully considered but is not found to be persuasive. Rampart et al. found that IL-8 induced plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. specifically determined the type of immune cells that were recruited (neutrophils). The instant specification does not report what type(s) of immune cells were recruited by PRO331. Also, Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that

substantial further work would have been required to confirm that speculation. In this specific case, human PRO331 was found to be an irritant to guinea pigs. Such *might* indicate that PRO331 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO331, e.g. that the human PRO331 protein has an epitope that the guinea pigs were pre-sensitized to, or that the guinea pigs' bodies recognized PRO331 as a foreign substance, irritant, or toxin. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO331. Accordingly, the only inflammation that could be treated using anti-PRO331 agents at the time the invention was made is that actually caused by PRO331, which is a circular exercise with no meaning, as there is no reason to believe that any patient has any condition resulting from excess PRO331 based upon the results in the specification as originally filed. It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptides.

At the second paragraph of p. 11 of the response, Appellants refer to the declaration of Dr. Fong (filed under 37 C.F.R. 1.132 on 30 September 2004). Appellants argue that Dr. Fong is an expert in the field of immunology, an inventor, and an experienced scientist familiar with the SVP assay (a characterization with which the examiner takes no issue). Appellants quote from point 7 of the declaration. Appellants argue that a positive score in the SVP assay indicates that PRO331 polypeptides have

utilities including treatments of autoimmune diseases, psoriasis, and others, as discussed in the Fong declaration. Appellants urge that such utilities would be understood, appreciated, and accepted by those skilled in the art as substantial, specific, and credible. This has been fully considered but is not found to be persuasive. Point 7 of the Fong declaration reads as follows:

> 7. Proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. These proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. These cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. How leukocytes exit the vasculature and move to these appropriate destination of injury or infection is critical and tightly regulated. Leukocytes move from the blood vessel to injured or inflamed issues by rolling along the endothelial cells of the blood vessel wall and then extravasate through the vessel wall and into the tissues (see Exhibit B). This diapedesis and extravasation step involves cell activation and a stable leukocyte-endothelial cell interaction.

This section only generally explains some mechanisms of inflammation. However, it does not explain how the skilled artisan is to use molecules inducing such inflammation. For example, poison ivy extract, splinters, spider venom, and proteins from heterologous organisms would all test positive in the SVP assay, and generally induce pathways discussed in point 7. However, the skilled artisan would not use such therapeutically. Also, Appellants' argument that a positive result in the assay indicates therapeutic usefulness to treat inflammatory disease makes no sense. One skilled in the art would not inject an irritant or a pro-inflammatory substance to treat inflammation. Furthermore, one skilled in the art would not assume that a substance testing positive in

the assay plays any role in inflammatory diseases such as psoriasis and inflammation without further testing.

2. Appellants argue that the examiner's characterization of the PRO331 polypeptides does not negate their utility. Leading into the second line of argument at p. 12 of the Brief, Appellants argue that the examiner's characterization of the assay as one that screens for irritants is without evidentiary or literature support. Appellants argue that the examiner's concerns that lye or acid would test positive in the assay are unfounded, since the assay uses a buffered pH of about 6.8. Appellants refer to point 6 of the Fong declaration, as well as pp. 186-188 as providing buffered PRO polypeptide samples. Appellants conclude that the PRO polypeptides are not basic irritants in that they are buffered to be neutral. This has been fully considered but is not found to be persuasive. The SVP assay at pp. 210-211 of the specification does not indicate that a buffer system was used. Pages 186-188 of the specificaiton do not mention buffers. Therefore, Appellants' argument is without support. Furthermore, pH-neutral irritants would also test positive in this assay. For example, poison ivy extract, splinters, rusty nails, insect saliva, thorns, spider/snake/bee sting venom, etc., all would test positive in the assay. Nevertheless, such substances are not considered to be therapeutically beneficial as pro-inflammatory agents.

At the bottom of p. 12 of the Brief, Appellants argue that PRO331 is not merely an irritant. Specifically, Appellants point to the examiner's statement in the 23 December 2004 Office Action that PRO331 polypeptides induce inflammation in an animal model, and that the results *might* indicate that PRO331 is an inflammatory

cytokine. Appellants urge that the skilled artisan would consider it more likely than not that the PRO331 polypeptides are able to induce inflammation; and thus can be used to induce inflammation when desired or to make antibodies that inhibit inflammation when desired. This has been fully considered but is not found to be persuasive. An animal often experiences an inflammatory response when a foreign substance is introduced into the body, whether by injury or infection or ingestion, etc. However, the skilled artisan would not use just any foreign substance to induce inflammation without further research to determine exactly what sort and what magnitude of immune response is generated. Also, the assay provides no information regarding which inflammatory diseases, if any, involve PRO331. Due to the large quantity of experimentation necessary to determine how to use the claimed polypeptides other than as a polypeptide having the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells; the lack of direction/guidance presented in the specification regarding other uses, including uses related to vascular permeability activity as discussed above; the absence of working examples directed to PRO331 polypeptides having specifically useful pro-inflammatory activities; the complex nature of the invention; the contradictory state of the prior art; the unpredictability of what activities any uncharacterized protein may have; and the breadth of the claims which fail to recite useful functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

From p. 13 to p. 14 of the Brief, Appellants urge that the examiner's arguments regarding a potential allergic reaction to PRO331 do not negate utility. Appellants argue

that it is more likely than not that guinea pigs are not allergic to PRO331, since an allergic reaction would have required that the guinea pigs had been pre-exposed to PRO331. Appellants also urge that, even if the guinea pigs had experienced an allergic reaction to the PRO331, such would still demonstrate utility of the PRO331 polypeptides, since they induced an inflammatory response. Appellants conclude that the PRO331 polypeptides could be used to induce inflammation, and that PRO331 antibodies could be used to suppress an allergic response to PRO331. This has been fully considered but is not found to be persuasive. First, the guinea pigs would have had to have been previously exposed to a substance that shared an epitope with PRO331, and need not have been exposed to PRO331 *per se*. For example, people who are allergic to penicillin are generally allergic to all antibiotics of that class, even when the structures are not identical. Also, there is no evidence of record that skilled artisans (e.g., physicians) use allergens to induce a desired inflammatory response (e.g., such as for an infected, recalcitrant leg ulceration). The examiner's previous mention of a possible allergic response was made to illustrate that a positive result in the SVP assay does not indicate that it is more likely than not that the tested molecule is a pro-inflammatory cytokine. A positive result in the SVP assay can indicate that the tested molecule is a pro-inflammatory cytokine OR an allergen OR an irritant OR a toxin, etc. The art shows that the skilled artisan does not rely on a positive result in the assay alone to conclude that a molecule plays a role in inflammation. See Barsoun et al., Szalai et al., and Rampart et al.

3. Appellants argue that the examiner has not rebutted the evidence and arguments that support the asserted utility. At pp. 14-15 of the Brief, Appellants review the Fong declaration in depth. Appellants urge that the examiner has not considered this evidence. This has been fully considered but is not found to be persuasive. The Office Action of 23 December 2004 addressed the Fong declaration in depth. The comments made therein are imported herein as follows:

> In the declaration, items 1-9, Dr. Fong states that Assay # 64 is known as the Miles assay and is well known in the art as an assay to identify proinflammatory molecules. Declarant states that proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. Declarant states that these proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. Declarant states that these cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. Declarant states that these processes are critical and tightly regulated via diapedesis and extravasation steps. Declarant concludes that proinflammatory molecules are useful in treating infections, as local administration of the proinflammatory polypeptide would stimulate immune cells already present at the site of infection and induce more immune cells to migrate to the site, thus removing infection at a faster rate. Declarant points to MCP-1 and MCP-2 as being useful to cause neutrophils to extravasate, other CXC chemokines as being useful to activate neutrophils, and other CXC chemokines as being useful to cause chemotaxis of T lymphocytes. Declarant states that inhibitors of proinflammatory molecules are useful to treat diseases characterized by abnormal immune cell response. Declarant states that proinflammatory molecules with angiostatic properties are useful in treating tumors. Declarant states that the Miles assay was initially developed when researching the effect of histamine on the vascular system. Declarant states that subsequent workers have developed the assay into a quantitative one. This has been fully considered but is not found to be sufficient to overcome the rejection. The Miles assay is useful as a preliminary screen for potential proinflammatory molecules. Basic irritants, such as lye, would test positive in the Miles assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may e useful as a proinflammatory. For example, MCP-1 and MCP-2 are not only positive in the Miles assay, they were also shown to have the specific activity of causing the extravasation of neutrophils. As Declarant points out, other CXC cytokines, while scoring positive in a Miles assay, have subsequently been shown to have specific activities of

activating neutrophils or being chemotactic for T lymphocytes. As was discussed in the previous Office Action, the state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule is a proinflammatory molecule with specific activities, as opposed to a basic irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound. For example, the Rampart reference (Am. J. Pathol. 135:21, 1989) is one in which IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation.

In point 10, Declarant states that the skin vascular permeability assay was used to determine if blood coagulation factor XIII (FXIII) could be used in treating Shonlein Henoch Purpura (SHP). Declarant refers to Hirahara et al. (1993, Thrombosis Res. 71:139-148) as showing that FXIII stabilized microvasculature, leading to less permeability, and therefore may be useful in treatment of SHP. This has been fully considered but is not found to be sufficient to overcome the rejection. In the instant case, the claimed PRO protein tested positive in the assay. FXIII tested negative. Therefore, the results are not comparable.

In point 11, Declarant states that the Miles assay was used by Senger et al. (1983, Science 219:983-985) to show that a secreted factor called VPF caused vascular permeability. This has been fully considered but is not found to be sufficient to overcome the rejection. Senger et al. set out to determine why vessels lining the peritoneal cavities of rodents with ascites tumors display markedly greater permeability than vessels in control animals. Senger et al. only conclude that secretion of permeability-increasing activity appears to be a common feature of tumor cells and that VPR has permeability-increasing activity. Senger et al. do not suggest that VPR can be considered a pro-inflammatory molecule useful for treatment of injury or infection.

In point 12, Declarant states that Yeo et al. (1992, Clin. Chem. 38:71-75) confirmed the viability of the skin vascular permeability assay by correlating it with disassociation enhanced lanthanide fluoroimmunoassay (DELFIA) results. Declarant states that VPF (VEGF) tested positive in the skin vascular permeability assay and then anti-VPF antibodies were used to quantify the amount of VPF in the DELFIA. Declarant states that the DELFIA assay has greater sensitivity. This has been fully considered but is not found to be sufficient

to overcome the rejection. Yeo et al. do not assert that the DEFLIA assay or the Miles assay can be used to identify proinflammatory molecules that can be used to treat injury or infection. Yeo et al. disclose that VPF may be the same protein as VEGF, which has been shown to be a mitogen specific for endothelial cells, and may promote tumor angiogenesis via its mitogenic activity for endothelial cells. However, the specific and useful activity of VEGF as an angiogenic factor was not identified by the Miles assay or the DEFLIA assay. Significant further research had to be conducted to identify this specific and substantial activity.

In point 13, Declarant reviews the skin vascular permeability assay and refers to Exhibit I as showing a positive reaction for a PRO polypeptide. This has been fully considered but is not found to be sufficient to overcome the rejection. It is not clear that the PRO polypeptide shown in the exhibit is the same PRO polypeptide of the instant claims. Furthermore, the assay does not provide the skilled artisan with the guidance necessary for the skilled artisan to determine how to use the claimed PRO polypeptide without resorting to undue experimentation.

In point 14, Declarant provides his expert opinion that the PRO polypeptide that shows activity in the skin permeability assay has specific, substantial and credible utilities. Declarant states that the application discloses that the results of the skin permeability assay were further analyzed by histopathological examination to rule out inflammation due to endothelial cell damage or mast cell degranulation. Declarant concludes that the vascular permeability observed was not due to histamine release or endothelial cell damage. Declarant asserts that the PRO polypeptides testing positive in the assay are useful to enhance immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases. Declarant further states that angiogenic or angiostatic properties of proinflammatory would find utility in controlling tumorigensis. This has been fully considered but is not found to be sufficient to overcome the rejection. The specification describes analysis of the results of the skin vascular permeability assay as follows:

> The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

As this quotation shows, the Declarant is not entirely correct with respect to the facts. The PRO polypeptides used in the assay are not further analyzed by histopathological examination **to rule out inflammation due to endothelial cell damage or mast cell degranulation**. In this specific case, human PRO331 was found to be an irritant to guinea pigs. Such *might* indicate that PRO331 is an

> inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO331, e.g. that the human PRO331 protein has an epitope that the guinea pigs were pre-sensitized to. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO331. Accordingly, the only inflammation that could be treated using anti-PRO331 agents at the time the invention was made is that actually caused by PRO331, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting from excess PRO331 based upon the results in the specification as originally filed). It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptides. Finally, Declarant's comments regarding angiogenic or angiostatic activities of the PRO polypeptides is off-point, since these activities were not disclosed in the specification. Finally, it is noted that opinion declarations are evaluated for the reasonableness and validity of the opinion; however, no weight is given to an opinion on the ultimate legal conclusion in issue. Enablement is a legal conclusion. See *In re Lindall*, 155 USPQ 521; *In re Chilowsky*, 134 USPQ 515.
>
> Due to the large quantity of experimentation necessary to determine how to use the claimed polypeptides other than as a polypeptide having the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells; the lack of direction/guidance presented in the specification regarding other uses, including uses related to vascular permeability activity as discussed above; the absence of working examples directed to PRO331 polypeptides having specifically useful pro-inflammatory activities; the complex nature of the invention; the contradictory state of the prior art; the unpredictability of what activities any uncharacterized protein may have; and the breadth of the claims which fail to recite useful functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

At pp. 15-16 of the Brief, Appellants discuss the legal standards for reviewing evidence. This has been fully considered but is not found to be persuasive. Regarding *In re Rinehart* and *In re Alton*, the instant rejection is being maintained upon a fresh consideration of all of the evidence of record, and the rejection is being maintained in view of the examiner's determination that the preponderance of the totality of the evidence supports the maintenance of the rejection, as discussed herein. Also

regarding *In re Alton*, the examiner *has* considered the opinion evidence. Regarding the Utility Examination Guidelines, the opinion has not been disregarded; it has been considered along with the other evidence of record. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the fact sought to be established is whether or not a positive result in the SVP assay indicates a therapeutically important role for the tested substance. This is a fairly complex issue. Second, strong opposing evidence has been brought forth on the record that a positive result in the assay is a preliminary result, since irritants and toxins also test positive in the assay and are not thought to be therapeutically useful as a result (Barsoun et al., Szalai et al., Rampart et al.). Dr. Fong is one of the inventors and has an interest in the outcome of the case, as opposed to a disinterested expert in the field. Finally, Dr. Fong bases his conclusions on facts. However, it is believed that the opposing evidence and scientific reasoning counterbalance the evidence contained in the declaration.

In the second paragraph of p. 16 of the Brief, Appellants argue that a positive result in the assay establishes an inflammatory utility for the claimed polypeptides, and the specification enables the skilled artisan to use the polypeptides for the asserted

purpose. Appellants argue that publications and testimony have been submitted as evidence to support the asserted utility. Appellants urge that the skilled artisan would find it more likely than not that PRO331 polypeptides are useful for inducing inflammation, and PRO331 antibodies could be used to inhibit inflammation. This has been fully considered but is not found to be persuasive. The SVP assay merely indicates that PRO331 was found to be an irritant to guinea pig skin. Due to the large quantity of experimentation necessary to determine how to use the claimed polypeptides other than as a polypeptide having the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells; the lack of direction/guidance presented in the specification regarding other uses, including uses related to vascular permeability activity or pro-inflammatory activity as discussed above; the absence of working examples directed to PRO331 polypeptides having specifically useful pro-inflammatory activities; the complex nature of the invention; the contradictory state of the prior art (Barsoun et al., Szalai et al., Rampart et al.); the unpredictability of what activities any uncharacterized protein may have; and the breadth of the claims which fail to recite useful functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

4. Appellants argue that the SVP assay is a robust assay that may be used to identify both inflammatory and anti-inflammatory molecules. At p. 16 of the Brief, Appellants take issue with the examiner's characterization of the Hirahara et al. reference (cited in the Fong declaration) as not being comparable to those of the instant

application since PRO331 tested positive in the assay whereas FXIII tested negative. Appellants argue that the specification and Hirahara et al. constitute evidence that both positive and negative results in the SVP assay establish utility as pro-inflammatory molecules and anti-inflammatory molecules, respectively. This has been fully considered but is not found to be persuasive. PRO331 did not test negative in the assay. Therefore, whether or not a molecule testing negative in the assay establishes a utility is off-point.

5. Appellants argue that the mechanism of an asserted utility need not be understood nor need the utility be superior to other methods of attaining that utility. At pp. 17-18 of the Brief, Appellants take issue with the examiner's statement that a positive result in the SVP assay is merely a jumping-off point, or an invitation to further experiment to determine the properties of PRO331. Appellants argue that a positive result in the SVP assay indicates induction of inflammation, and that the skilled artisan would have believed it more likely than not that the PRO331 polypeptides were useful for their asserted utility (as pro-inflammatory molecules). This has been fully considered but is not found to be persuasive. The disclosed SVP assay did not report results compared to controls, and indicated that even a "minimal perivascular infiltrate at the injection site is scored as positive." The identity of the cells types at the injection site was not disclosed. Clearly, the disclosed results are preliminary, and significant further research would be required from the skilled artisan to determine what type of immune response is induced by PRO331, and if it is any more significant than the immune response generated by an irritant or toxin.

At pp. 17-18 of the Brief, Appellants argue that the examiner inappropriately focuses on the underlying mechanism resulting in positive results in the SVP assay, and that there is no legal requirement for a specification to disclose a mechanism. Appellants also urge that the examiner is inappropriately concerned with the magnitude of the immune response. This has been fully considered but is not found to be persuasive. While it is true that a specification need not disclose a mechanism, a specification must teach the skilled artisan how to make and use a claimed invention in its full scope without requiring undue experimentation. In the instant case, the disclosed SVP assay and results are so devoid of detail that it amounts to an invitation to experiment with PRO331 to determine its significance and how it can be used.

C. Appellants argue that One Skilled in the Art would know how to make and use the variant proteins without undue experimentation based on the teachings in the art and in the specification At pp. 18-19 of the Brief, Appellants argue that a considerable amount of experimentation is legally acceptable if it is routine. Appellants urge that the claimed variants all must have the function of inducing an inflammatory response. Appellants refer to the specification's disclosure of the SVP assay as guidance for the skilled artisan to test for variants within the scope of the claims. Appellants refer to the specification's disclosure regarding how to calculate percent identity and preferred conservative amino acid substitutions as guidance for how to make and test the claimed variants. Appellants argue that the biological activity is not claimed based on structural similarity but instead on the positive results in the SVP assay. Appellants conclude that the specification provides ample guidance such that

the skilled artisan could easily test a variant polypeptide to determine whether it induces inflammation. Appellant also urges that the skilled artisan would know that production of antibodies to PRO331 polypeptides is useful since such antibodies have utility in the treatment of inflammation. This has been fully considered but is not found to be persuasive. "Make and test" is not the legal standard for enablement. The claims encompass a large number of structural variants, having at least 80% amino acid identity to the extracellular domain of PRO331. It is mathematically improbable that the extracellular domain alone would test positive in any of the assays described, including the inhibition of VEGF stimulated endothelial cell proliferation and endothelial cell apoptosis assays, since an isolated extracellular domain is missing more than half of the full length or mature protein that was tested in any of the assays. It would involve a tremendous quantity of experimentation to make and test variants polypeptides *comprising* a sequence having at least 80% amino acid identity to the extracellular domain of PRO331, since the breadth of the genus is infinite. Furthermore, there are no working examples or specific guidance to particular, active variants of PRO331. The issue of whether or not variant polypeptides retain the function of the unaltered, starting polypeptides is unpredictable and complex, as discussed at p. 7 of the Office Action mailed 25 February 2003. In view of all of these factors, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Argument

Appellants have not requested to present an oral argument. However, in the event that Appellants request to do so in the future, the examiner wishes to present oral arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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